REMARKS

Prior to the present amendment, Claims1-10, 13-18, 21-29, 32-36, 44, 45, 48-68 and 75-78 were pending. In this amendment Claims 1, 9, 16, 18, 24, 26, 28, 36, 60, and 75 are amended. Claims 2, 6, 8, 10, 17, 25, 27, 35, 37-59, and 61-74 are cancelled. New claims 79-80 are presented. Claims 1, 3-6, 7, 9, 13-16, 18, 21-24, 26, 28-29, 32-34, 36, 60, and 75-80 remain in prosecution.

SEQ ID NO: and Amendments to the Specification

There has been a considerable amount of confusion concerning the use of SEQ ID in this case. In the immediately previous Amendment Applicants attempted to amend a SEQ ID into the Specification based on a Genbank Accession Number. As pointed out in the Office Action, the listed GenBank Accession Number pointed to a sequence that was not at all appropriate. The matter of the correct GenBank Number is addressed immediately below. However, Applicants also understand the Examiner to be stating that the addition of a SEQ ID NO based even on a perfectly appropriate GenBank Number would not be proper. Because much may turn on this choice, Applicants wish to explain their current understanding of the situation. If Applicants' understanding is incorrect, they would appreciate a correction from the Examiner.

Applicants now understand that use of the GenBank Number to add a SEQ ID NO is not proper for at least two reasons. A primary problem is that such addition would have to be based upon an incorporation by reference. The rules indicate that any incorporation by reference requires an explicit statement in the originally filed specification. Since the original specification appears to lack such a statement, the content of the reference (the GenBank Number) cannot be relied upon. Further, even if an incorporation by reference had been included in the original specification, there would be some question as to whether the matter is

"essential." To the extent the matter is "essential" it would not be possible to follow the method attempted in the last amendment. Applicants had no intention to violate any rules.

The other problems with the sequence pointed out by the Examiner are due to a labeling error by the contract manufacturer of the gene arrays used in the test. Applicants ordered the construction of gene arrays based on their specifications. Essentially, the manufacturer constructs the arrays according to specified sequences and also includes a number of appropriate control sequences. The arrays are delivered with a spec. sheet listing the sequences used in the array construction. In the present case the manufacturer made a mistake and called out a sequence that, as pointed out by the Examiner, includes far more than the required sequence. In drafting the original specification the patent drafter had access to that spec. sheet and simply copied the mistake into the patent specification. Since Applicants cannot rely on that GenBank number (as explained above) this error has little outcome on allowability. However, when allowable matter is identified, this inadvertent error in the specification may cause confusion to those who read by the patent. While Applicants believe that a person of skill in the art would soon recognize that the listed GenBank Number is incorrect and would quickly find the correct GenBank Number, Applicants propose substituting the incorrect number with the more correct GenBank accession number NM_002290 [Homo sapiens laminin, alpha 4 (LAMA4), mRNA]. In terms of GenBank, this a "refseq" (referenced sequence) that has incorporated all earlier submissions; the entry also has citations to scientific papers about this laminin chain. This entry only contains mRNA sequence and a completely matching protein sequence information related to laminin $\alpha 4$ chain and is, therefore, completely $\alpha 4$ chain-specific. The replacement GenBank Number can be easily located by a person of skill in the art, and it includes the disclosed primers which were actually used to isolate and identify laminin $\alpha 4$ genetic material in the disclosed experiments.

Because this GenBank Number will not be relied upon for enablement, Applicants believe this amounts to the correction of an error and not the inclusion of new matter.

Amendments to the specification are made to include the new GenBank Number and to reverse the SEQ ID changes made in the previous amendment. If the Examiner believes the GenBank Number correction is inappropriate, the entire sentence referring to that number should be deleted from the Specification.

Rejections under 35 U.S.C. 112, first paragraph—Written Description.

In the Office Action the Examiner repeated the rejection of Claims 1-10, 13-18, 21-29, 32-36, 44-45, 48-68 and 75-78 under 35 U.S.C. 112, first paragraph as containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Applicants have now cancelled claims 2, 6, 8, 10, 17, 25, 27, 35, 44-52 and 61-68, which moots some of the rejections. The remaining claims have been amended so that the tumors involved are all brain tumors and more specifically glial tumors. Applicants believe that the Examiner agreed in an earlier paper that such tumors were properly enabled. To overcome the rejection based on the improperly included SEQ ID NO:1 specific laminin $\alpha 4$ RNA is now defined on the basis of amplification by the primer pair of SEQ ID NO:1 (original numbering) and SEQ ID NO:2. This is a highly specific primer pair and is known to amplify only nucleic acid specifically coding for human laminin $\alpha 4$. Since this pair identifies only that specific nucleic acid sequence and because the primers are completely defined in the specification Applicants respectfully request the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

As for the Examiner's concerns about mutations or splice variants, so far, no mutations of the human laminin α4 gene have been described. After the filing of the present patent, one splice variant of laminin α4 chain has been described in the literature (Hayashi Y, Kim KH, Fujiwara H, Shimono C, Yamashita M, Sanzen N, Futaki S, Sekiguchi K. "Identification and recombinant production of human laminin α4 subunit splice variants." Biochem Biophys Res Commun. 2002;299(3):498-504). This variant differs from the new GenBank Number by only 21 nucleotides (additional 7 amino acids are present in the protein). This region is outside of the mRNA sequence region where our primers for PCR detection of laminin α4 chain are located. Therefore, for any practical purposes, we will deal with total gene and protein using our tools described in the application. Further, the new splice variant has been detected in the literature as mRNA only. All protein work in the abovementioned reference paper was done using artificial transfection of cells with gene variant containing the extra sequence. Therefore, it is unknown if the longer splice variant is part of real α4 chain produced by the cells as part of a trimeric functional laminin. There are no other variations or mutations of the laminin α4 gene known. Rodent laminin α4 chain sequences also exist in GenBank but their sequences differ from that of *Homo sapiens* as represented by the new Genbank Number. The primers listed in the application will specifically detect mRNA fragment of human laminin α4 chain only.

As now claimed the invention is clearly enabled by the specification. The numerous figures demonstrate the increased expression of both the laminin α4 nucleic acid and the protein subunit in the case of malignant glial tumors. The protein subunit can be readily identified by one of skill in the art using antibodies while specific primer sequences are provided allowing one of skill in the art to verify that any particular nucleic acid (for example one visualized on a gel) is indeed the laminin α4 specific nucleic acid. In addition, the presented data demonstrate a clear relationship between overexpression of the markers and the potential of a

given tumor to invade and or reoccur. Thus tumors with identical cytological appearances can be ranked according to these properties. This is useful since a tumor with more potential to invade and/or reoccur should receive more extreme and aggressive medical treatment. It should be emphasized that the data are not hypothetical or merely academic. Currently the presented invention is the subject of successful ongoing clinical trials.

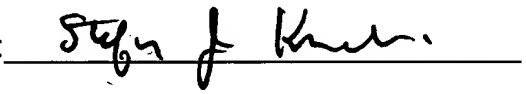
In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested. If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (310) 500-3548 to discuss the steps necessary for placing the application in condition for allowance.

You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No 50-2899.

Respectfully submitted,

LINER YANKELEVITZ SUNSHINE & REGENSTREIF LLP

Date: 21 March 2005

By: 

Stefan J. Kirchanski
Registration No. 36,568
Attorney for Applicants

1100 Glendon Ave., 14th Floor
Los Angeles, CA 90024
Telephone: (310) 500-3500
Facsimile: (310) 500-3501